Clioquinol (Iodochlorhydroxyquin, Vioform) and Iodoquinol (Diiodohydroxyquin): Blindness and Neuropathy

Committee on Drugs

Clioquinol and iodoquinol are found in topical compounds for dermatologic use. Their application in pediatrics has been for treatment of diaper dermatitis, although the current labeling for these products advises against their use in children younger than 2 years of age. The Table lists a few of the many agents currently available that contain clioquinol or iodoquinol. Some nonprescription products also contain clioquinol.

Since our 1974 commentary on the toxicity of these drugs to children, additional reports of toxicity following skin application have become available. Both clioquinol and iodoquinol have been known to cause serious and irreversible optic atrophy and peripheral neuropathy. This class of drugs was associated with several thousand cases of subacute myelo-optic neuropathy in Japan. The clinical picture was that of a subacute onset of peripheral weakness and sensory loss, spastic paraparesis, and blindness, occurring in combination in various degrees. The most common symptoms were muscular weakness of the lower extremities and dysesthesia spreading to the trunk.

A World Health Organization committee convened in 1977 to prepare a list of essential drugs and excluded clioquinol because it considered the risks of treatment greater than the potential benefit. Other authoritative sources of drug information state that “clioquinol has limited topical antibacterial and antifungal activity” and that “routine use of either compound (clioquinol or iodoquinol) is not recommended.”

A recent clinical study examined the percutaneous absorption of clioquinol. Five healthy male subjects received one application (5 g) of 3% clioquinol cream applied for 12 hours to a 200 cm² area of the forearm (1.1% of body surface area). The skin was occluded with Saran Wrap and gauze. Approximately 40% of the dose was absorbed during the 12 hours, ie, about 60 mg of clioquinol. Plasma concentrations of 0.37 to 0.56 mg/L were detected within 2 hours. Although the remainder of the cream was removed after 12 hours, plasma levels remained elevated for an additional 12 hours.

The concentrations in this study are comparable to the clioquinol plasma levels of 0.29 to 0.52 mg/L measured in five dogs on whom 3% clioquinol cream (5 g twice daily) was applied topically for 28 days. In this study, approximately 50% of the clioquinol was absorbed during a 16-hour period. During a 28-day observation period, all dogs were lethargic, less responsive to stimuli, and experienced an average weight loss of 15%. Three of the five dogs developed dermatitis; one dog died 15 days after treatment ended. Examination of the liver demonstrated diffuse centrilobular and midzonal cell necrosis, suggesting hepatocellular toxicity. Partial hind limb paralysis was seen in one dog.

Use of these drugs in infants carries a risk of toxicity. Application of 1 g of 3% clioquinol cream three times a day to the skin of an infant weighing 10 kg would result in a dose of 9 mg/kg per day. This is similar to the 17 mg/kg per day dose applied to the dogs, and it is more than three times greater than the single 2.5 mg/kg dose used in the clinical study. Of additional concern is the well-known fact that greater drug absorption occurs through inflamed skin than through normal skin. Drug absorption also is enhanced when applied under an occlusive dressing, such as diapers.

Alternative topical agents for dermatitis exist that have less risk of toxicity. For primary irritant dermatitis in which evidence for prostaglandin generation has been obtained, "frequent applications of a bland protective topical agent (petrolatum or zinc oxide paste) following thorough gentle cleansing may suffice to prevent dermatitis." For secondary infection, "Polysporin (polymixin B plus bacitracin) and bacitracin are probably the two..."
TABLE.  Partial List of Products Containing Clioquinol and Iodoquinol*

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clioquinol cream, ointment</td>
<td>Vioform</td>
<td>CIBA</td>
</tr>
<tr>
<td>Clioquinol and hydrocortisone cream, lotion, ointment</td>
<td>Vioform-Hydrocortisone</td>
<td>CIBA</td>
</tr>
<tr>
<td>Iodoquinol and hydrocortisone cream</td>
<td>Vytone</td>
<td>Dermik</td>
</tr>
<tr>
<td>Iodoquinol and hydrocortisone</td>
<td>Iodo-Cortifair</td>
<td>Pharmafair</td>
</tr>
<tr>
<td>Iodoquinol tablets</td>
<td>Yodoxin</td>
<td>Glenwood</td>
</tr>
</tbody>
</table>

* More than 50 other products containing clioquinol or iodoquinol are registered with the Food and Drug Administration.

most useful preparations for pyoderma.”13 Topically applied nystatin is specific for Candida superficial fungal skin infections. Haloprogin, miconazole, clotrimazole, and econazole are active against Candida, Pityrosporum orbiculare, and the dermatophytes. Topical antibiotic combinations with other agents, such as corticosteroids, in general are inadvisable.13

CONCLUSION

Clioquinol and iodoquinol are neurotoxic. Their use for topical application poses a potential risk of toxicity to infants and children. Since alternative effective treatments for dermatitis are available, we recommend that drug products containing clioquinol or iodoquinol not be used.

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